REMARKS

Claims 26, 28-31, and 44-59 were previously pending and under examination. Claims 26, 46, and 53 have been amended herein. Support for the amendments can be found throughout the specification and claims as filed. More particularly, support can be found, *e.g.*, in paragraphs [0040], [0166], and [0171] of the specification as published (US 2008/0058431). No new matter has been added by the amendments.

Objection

Claims 53-59 have been objected to for reciting a mouse "comprising" rather than a mouse "exhibiting" an increased body weight. *See Office Action* at p. 2. Applicants have amended Claim 53 and claims dependent therefrom (*i.e.*, Claims 54-59) to recite a mouse "exhibiting" an increased body weight, and therefore respectfully request withdrawal of the pending objection.

Rejections under 35 U.S.C. § 112, First Paragraph – Enablement

The Examiner has maintained the rejection of Claims 26, 28-31, and 44-52 under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide enablement for the full scope of the claims. The Examiner asserts that the claims encompass mice "that have a disruption in the Shp2 gene in all cells of the mouse or in cells other than cells of the forebrain." *Office Action* at p. 3. The Examiner also cites Grossman *et al.* (PNAS, 2009, 106:16704-16709, hereinafter "Grossman"), Nakamura *et al.* (PNAS, 2009, 106:11270-11275, hereinafter "Nakamura"), and Saxton *et al.* (1997, EMBO J, 16:2352-2364, hereinafter "Saxton") as teaching conditional knockouts of Shp2 that lead to phenotypes other than those in the present claims. *See Office Action* at pp. 3-4.

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *M.P.E.P.* § 2164.01(b), citing *In re Fisher*, 427 F.2d 833 (CCPA 1970). The evidence provided by an applicant "need not be conclusive but merely convincing to one skilled in the art." *Id.* (underline in original).

Applicants may cite references to show what one of skill in the art knew at the time of filing the application. *See id.*

The references cited by the Examiner disclose conditional mutations of Shp2 using the Wnt1-cre promoter, which introduces recombination in neural crest cells (NCCs). *See Grossman* at p. 16704. As one of skill in the art would have recognized at the time of filing, NCCs are migratory cells that give rise to melanocytes, connective tissue of the head, and glial and neuronal cells of the peripheral nervous system. *See Grossman* at p. 16704 (of record). In the references cited by the Examiner, conditional mutations of Shp2 in neural crest cells resulted in heart and craniofacial abnormalities, and a conditional mutation of Shp2 in myelinating Schwann cells resulted in reduced myelination of peripheral nerves. *See Nakamura* at Abstract; *Grossman* at pp. 16705-16706. Further, non-conditional mutations of Shp2 in embryonic stem cells resulted in embryonic lethality, with embryos failing to properly gastrulate. *See Saxton* at p. 2352. One of skill in the art at the time of filing would have therefore have predicted that the conditional knockout of Shp2 in neural crest cells would lead to abnormal phenotypes outside of the forebrain, and that a germline knockout of Shp2 would lead to embryonic lethality.

In contrast, the present claims are directed to a genetically modified mouse whose genome comprises a homozygous disruption of the endogenous Shp2 gene in neuronal forebrain cells. Without acquiescing to the rejection, and solely to advance prosecution, Applicants have amended the claims to clarify that "cells outside of the forebrain do not have a homozygous disruption of the endogenous Shp2 gene" in Claim 26, and to clarify that "cells outside of the forebrain are not genetically altered to lack expression of the endogenous Shp2 gene" in Claim 46. As such, the amended claims do not recite a mouse with "a disruption in the Shp2 gene in all cells of the mouse or in cells other than cells of the forebrain," as asserted by the Examiner.

The instant Specification teaches one of skill in the art to generate a genetically modified mouse specifically lacking Shp2 expression in neuronal forebrain cells that exhibits an increased body weight compared to a wild-type mouse. For example, the instant Specification teaches one of skill in the art to generate such a mouse by breeding $Shp2^{flox/+}$ mice with CamK2a-Cre transgenic mice. *See Specification* at Example 1, paragraphs [0031]-[0037], and Figures 1-7. Further, Applicants respectfully submit that one of skill in the art at the time of filing would have known other neuron-specific promoters (*i.e.*, other than CamK2a) that could be used to generate

a genetically modified mouse specifically lacking expression in forebrain cells. For example, one of skill in the art would have recognized pro-opiomelanocortin (POMC) and murine neurofilament-H (mNF-H) as neuron-specific promoters. *See, e.g., Heisler et al.*, Science 297: 609-611 (2002); *Hirasawa et al.*, Neuroscience Research 40: 125-132 (2001). One of skill in the art could have therefore predictably arrived at the claimed phenotypes without undue experimentation using the teachings in the Specification and knowledge in the art at the time of filing.

For at least these reasons, Applicants submit that the full scope of the claims is enabled, and therefore respectfully request that the Examiner withdraw the rejection of Claims 26, 28-31, and 44-52 under 35 U.S.C. § 112, first paragraph.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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